

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/44, 38/28 // (A61K 38/28, 31:44)	A1	(11) International Publication Number: WO 98/57636 (43) International Publication Date: 23 December 1998 (23.12.98)
(21) International Application Number: PCT/EP98/03692		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 15 June 1998 (15.06.98)		
(30) Priority Data: 9712866.4 18 June 1997 (18.06.97) GB		(72) Inventor; and (75) Inventor/Applicant (for US only): SMITH, Stephen, Alistair [GB/GB]; Smithkline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).
(74) Agent: RUTTER, Keith; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: TREATMENT OF DIABETES WITH ROSIGLITAZONE AND INSULIN		
(57) Abstract <p>A method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of Compound (I) and insulin to a mammal in need thereof.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

TREATMENT OF DIABETES WITH ROSIGLITAZONE AND INSULIN

This invention relates to a method of treatment, in particular to a method for the treatment of diabetes mellitus, especially non-insulin dependent diabetes (NIDDM) or
5 Type II diabetes and conditions associated with diabetes mellitus.

Insulin is a front line treatment agent for Type I diabetes (or Insulin Dependent Diabetes). It is also used as an antihyperglycaemic agent in the treatment of NIDDM.

European Patent Application, Publication Number 0,306,228 relates to certain
10 thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

15 International Patent Application, publication number WO97/05875 discloses a method for reducing the amount of exogenous insulin administered to a patient having NIDDM by administering a therapeutically effective amount of a thiazolidinedione derivative and/or a related compound.

It is now surprisingly indicated that a specific amount of Compound (I) in
20 combination with insulin provides a particularly beneficial effect on glycaemic control, such combination is therefore particularly useful for the treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus.

Accordingly, the invention provides a method for the treatment of diabetes mellitus, especially Type II diabetes and conditions associated with diabetes mellitus
25 in a mammal such as a human, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of Compound (I) and insulin, to a mammal in need thereof.

Preferably, the amount of Compound (I) administered is up to 12 mg, especially when administered per day.

30 The method comprises either co-administration of Compound (I) and insulin or the sequential administration thereof.

Co-administration includes administration of a formulation which includes both an insulin sensitiser, such as Compound (I), and insulin or, more suitably, the essentially simultaneous administration of separate formulations of each
35 agent.

In one particular aspect, the method comprises the administration of 2 to 12 mg of Compound (I), especially when administered per day.

Particularly, the method comprises the administration of 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I) per day.

Particularly, the method comprises the administration of 2 to 4mg of Compound (I), especially when administered per day.

5 Particularly, the method comprises the administration of 4 to 8mg, such as greater than 4 for example 4.1, to 8 mg, of Compound (I), especially when administered per day.

Particularly, the method comprises the administration of 8 to 12 mg of Compound (I), especially when administered per day.

10 Preferably, the method comprises the administration of 2 mg of Compound (I), especially when administered per day.

Preferably, the method comprises the administration of 4 mg of Compound (I), especially when administered per day.

15 Preferably, the method comprises the administration of 8 mg of Compound (I), especially when administered per day.

It will be understood that Compound (I) and the insulin are each administered in a pharmaceutically acceptable form, including for Compound (I), pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts and solvates thereof.

20 Suitable pharmaceutically acceptable salted forms of Compound (I) include those described in EP 0306228 and WO94/05659. A preferred pharmaceutically acceptable salt is a maleate.

Suitable pharmaceutically acceptable solvated forms of Compound (I) include those described in EP 0306228 and WO94/05659, in particular hydrates.

25 Suitable pharmaceutically acceptable forms of insulin are referred to in standard reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.) and Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein).

30 Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

35 Compound (I) may exist in one of several tautomeric forms, all of which are encompassed by the term Compound (I) as individual tautomeric forms or as mixtures thereof. Compound (I) contains a chiral carbon atom, and hence can exist in one or more stereoisomeric forms, the term Compound (I) encompasses all of these isomeric forms whether as individual isomers or as mixtures of isomers, including racemates.

Insulin is prepared according to known methods, such methods are found or are referred to in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.) and Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st 5 Edition page 341 and pages cited therein).

When used herein the term 'conditions associated with diabetes' includes conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

'Conditions associated with diabetes mellitus itself' include hyperglycaemia, 10 insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational diabetes.

15 'Complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy.

Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

20 As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinarianily acceptable compound.

For the avoidance of doubt, when reference is made herein to scalar amounts, including mg amounts, of Compound (I) in a pharmaceutically acceptable form, the 25 scalar amount referred to is made in respect of Compound (I) *per se*: For example 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt which contains 2 mg of Compound (I).

Diabetes mellitus is preferably Type II diabetes.

The particularly beneficial effect on glycaemic control provided by the 30 treatment of the invention is indicated to be a synergistic effect relative to the control expected for the sum of the effects of the individual active agents.

Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (Hb A1c). Such indices are 35 determined using standard methodology, for example those described in: Tuescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 and 390 and Frank P., 'Monitoring the Diabetic Patent with Glycosolated Hemoglobin Measurements', Clinical Products 1988

In a preferred aspect, the dosage level of each of the active agents when used in accordance with the treatment of the invention will be less than would have been required from a purely additive effect upon glycaemic control.

5 In the method of the invention, the active medicaments are preferably administered in pharmaceutical composition form. As indicated above, such compositions can include both medicaments or one only of the medicaments.

10 In the treatment of the invention, insulin is usually administered by injection or by other known methods, for example those described in the reference texts mentioned herein. Thus the following comments relating to compositions, formulations and methods of administration suitably refer to the compositions, formulations and administration of Compound (I).

Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

15 The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

20 Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

30 Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan

monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the Compound (I)s suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Compositions may contain from 0.1% to 99% by weight, preferably from 20 10-60% by weight, of the active material, depending upon the method of administration.

Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The compositions are formulated according to conventional methods, such as those disclosed herein and in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.) and Martindale The Extra Pharmacopoeia (London The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books).

30 The compositions are preferably in a unit dosage form in an amount appropriate for the relevant daily dosage.

Suitable dosages including unit dosages of the Compound of formula (I) comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

In the treatments the two medicaments may be administered from 1 to 6 35 times a day, but most preferably 1 or 2 times per day.

Suitable dosages of insulin, including unit dosages, include those described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.) and Martindale The

Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein).

A range of 2 to 4mg includes a range of 2.1 to 4, 2.2 to 4, 2.3 to 4, 2.4 to 4, 2.5 to 4, 2.6 to 4, 2.7 to 4, 2.8 to 4, 2.9 to 4 or 3 to 4mg.

5 A range of 4 to 8mg includes a range of 4.1 to 8, 4.2 to 8, 4.3 to 8, 4.4 to 8, 4.5 to 8, 4.6 to 8, 4.7 to 8, 4.8 to 8, 4.9 to 8, 5 to 8, 6 to 8 or 7 to 8mg.

A range of 8 to 12 mg includes a range of 8.1 to 12, 8.2 to 12, 8.3 to 12, 8.4 to 12, 8.5 to 12, 8.6 to 12, 8.7 to 12, 8.8 to 12, 8.9 to 12, 9 to 12, 10 to 12 or 11 to 12mg.

10 No adverse toxicological effects have been established for the compositions or methods of the invention in the abovementioned dosage ranges.

The following example illustrates the invention but does not limit it in any way.

COMPOUND (I) COMPOSITIONS**A Concentrate Preparation**

- 5 Approximately two thirds of the lactose monohydrate is passed through a suitable screen and blended with the milled maleate salt of Compound (I).
Sodium starch glycollate, hydroxypropyl methylcellulose, microcrystalline cellulose and the remaining lactose are passed through a suitable screen and added to the mixture. Blending is then continued. The resulting mixture is then wet
10 granulated with purified water. The wet granules are then screened, dried on a fluid bed drier and the dried granules are passed through a further screen and finally homogenised.

% COMPOSITION OF GRANULAR CONCENTRATE

15

Ingredient	Quantity (%)
Milled Compound (I) as maleate salt	13.25 (pure maleate salt)
Sodium Starch Glycollate	5.00
Hydroxypropyl Methylcellulose 2910	5.00
Microcrystalline Cellulose	20.0
Lactose Monohydrate, regular grade	to 100
Purified water	*

* Removed during processing.

20

B Formulation of the concentrate into tablets.

- The granules from above are placed into a tumble blender. Approximately two thirds of the lactose is screened and added to the blender. The microcrystalline cellulose, sodium starch glycollate, magnesium stearate and remaining lactose are screened and added to the blender and the mixture blended together. The resulting mix is then compressed on a rotary tablet press to a target weight of 150mg for the 1, 2 and 4mg tablets and to a target weight of 300mg for the 8mg tablets.
- 10 The tablet cores are then transferred to a tablet coating machine, pre-warmed with warm air (approximately 65°C) and film coated until the tablet weight has increased by 2.0% to 3.5%.

Tablet Strength	Quantity (mg per Tablet)			
	1.0mg	2.0mg	4.0mg	8.0mg
Active Ingredient:				
Compound (I) maleate Concentrate granules	10.00	20.00	40.00	80.00
Other Ingredients:				
Sodium Starch Glycollate	6.96	6.46	5.46	10.92
Microcrystalline Cellulose	27.85	25.85	21.85	43.70
Lactose monohydrate	104.44	96.94	81.94	163.88
Magnesium Stearate	0.75	0.75	0.75	1.50
Total Weight of Tablet Core	150.0	150.0	150.0	300.0
Aqueous film coating material	4.5	4.5	4.5	9.0
Total Weight of Film Coated Tablet	154.5	154.5	154.5	309.0

Claims

1. A method for the treatment of diabetes mellitus and conditions associated with diabetes mellitus in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amount of Compound (I) and insulin, to a mammal in need thereof.

5 2. A method according to claim 1, which comprises the administration of up to 12 mg of Compound (I).

10 3. A method according to claim 1 or claim 2, which comprises the administration of 2 to 12 mg of Compound (I).

15 4. A method according to any one of claims 1 to 3, which comprises the administration of 2 to 4, 4 to 8 or 8 to 12 mg of Compound (I).

5 5. A method according to any one of claims 1 to 3, which comprises the administration of 2 to 4mg of Compound (I).

20 6. A method according to any one of claims 1 to 3, which comprises the administration of 4 to 8mg of Compound (I).

7. A method according to any one of claims 1 to 3, which comprises the administration of 8 to 12 mg of Compound (I).

25 8. A method according to any one of claims 1 to 3, which comprises the administration of 2 mg of Compound (I).

9. A method according to any one of claims 1 to 3, which comprises the 30 administration of 4 mg of Compound (I).

10. A method according to any one of claims 1 to 3, which comprises the administration of 8 mg of Compound (I).

11. A pharmaceutical composition comprising Compound (I), insulin and a pharmaceutically acceptable carrier therefor.
12. A composition according to claim 11, wherein the insulin sensitiser is
5 Compound (I)
13. A composition according to claim 11 or claim 12, which comprises up to 12 mg or 2 to 12 mg of Compound (I).
- 10 14. A pharmaceutical composition comprising Compound (I), insulin and a pharmaceutically acceptable carrier therefor, for use as an active therapeutic substance.
15. A pharmaceutical composition comprising Compound (I), insulin and a pharmaceutically acceptable carrier therefor, for use in the treatment of diabetes mellitus and conditions associated with diabetes mellitus.

INTERNATIONAL SEARCH REPORT

Internat' Application No
PCT/EP 98/03692

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 A61K38/28 // (A61K38/28, 31:44)

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 10819 A (LIGAND PHARM INC) 27 March 1997 see page 2, line 2-15 see page 17, paragraph 1; claims 9-12, 18-20; table 1 compound BRL 49653 see page 7, line 1-13; figures 1A, 1B, 2A, 2B —	1-15
X	WO 95 07694 A (SANKYO CO ;GOODMAN HERBERT H (US)) 23 March 1995 formula 7 see page 26, line 26-30 see page 31; claim 23 see abstract —	1-15 —/—

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

16 October 1998

Date of mailing of the International search report

02/11/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03692

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 05875 A (WARNER LAMBERT CO ;WHITCOMB RANDALL W (US)) 20 February 1997 cited in the application Formula 7 see page 20, line 21; claim 21; example 1 see abstract ---	1-15
X	NEYROLLES N. ET AL: "New therapeutic agents of non insulin-dependent diabetes" ANNALES D'ENDOCRINOLOGIE, 1998, 59/2 (67-77), XP002080748 France see table 1 ---	1,11,12, 14,15
A	SKYLER J.S.: "Insulin therapy in type II diabetes: Who needs it, how much of it, and for how long?" POSTGRADUATE MEDICINE, 1997, 101/2 (85-90+92-94+96), XP002080749 USA see page 93, paragraph 2 see page 94, paragraph 2 ---	1-15
A	LEFEBVRE PJ ET AL: "Improving the action of insulin." CLIN INVEST MED, AUG 1995, 18 (4) P340-7, XP002080750 CANADA see abstract see page 342, column 2 ---	1-15
X	CONNOR SC ET AL: "Antidiabetic efficacy of BRL 49653, a potent orally active insulin sensitizing agent, assessed in the C57BL/KsJ db/db diabetic mouse by non-invasive ¹ H NMR studies of urine." J PHARM PHARMACOL, MAR 1997, 49 (3) P336-44, XP002080751 ENGLAND see abstract ---	1-15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/03692

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-10 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat. Application No

PCT/EP 98/03692

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9710819	A	27-03-1997	AU 7074296 A AU 7074496 A EP 0859608 A EP 0788353 A NO 981192 A WO 9710813 A AU 7362496 A NO 981501 A WO 9712853 A	09-04-1997 09-04-1997 26-08-1998 13-08-1997 18-05-1998 27-03-1997 28-04-1997 02-06-1998 10-04-1997
WO 9507694	A	23-03-1995	US 5478852 A AU 1770997 A AU 1771097 A AU 678291 B AU 7724994 A AU 679572 B AU 7835194 A CA 2168751 A CN 1131391 A CN 1134669 A CZ 9600722 A CZ 9600793 A CZ 9602822 A CZ 9602823 A EP 0719143 A EP 0719140 A FI 961213 A HU 75874 A HU 75873 A JP 9502722 T JP 9502727 T NO 961041 A NO 961052 A NZ 274346 A SK 35196 A WO 9507697 A US 5457109 A US 5602133 A	26-12-1995 29-05-1997 29-05-1997 22-05-1997 03-04-1995 03-07-1997 03-04-1995 23-03-1995 18-09-1996 30-10-1996 16-10-1996 16-10-1996 14-01-1998 14-01-1998 03-07-1996 03-07-1996 14-05-1996 28-05-1997 28-05-1997 18-03-1997 18-03-1997 14-05-1996 14-03-1996 24-06-1997 10-12-1997 23-03-1995 10-10-1995 11-02-1997
WO 9705875	A	20-02-1997	AU 6641196 A	05-03-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat : Application No

PCT/EP 98/03692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9705875 A		CA 2221241 A EP 0851757 A NO 980556 A	20-02-1997 08-07-1998 09-02-1998